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Individual maternal and child exposure to antibiotics in hospital – a national population-based validation study

Running head: Individual exposure to antibiotics in hospital

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Abstract

Aim

Exposure to antibiotics in early life may affect future health. The majority of antibiotics are prescribed in outpatient care, but inpatient exposure is also important. The aim of this study was to estimate how specific diagnoses in hospitals correspond to individual antibiotics exposure.

Methods

All pregnant women and children from birth to five-years-of-age with infectious diseases and other common inpatient diagnoses in the Swedish National Patient Register between July 2005 and November 2011 were identified. Random samples of individuals from pre-defined groups were drawn and medical records requested from the clinics manually reviewed for information on antibiotics.

Results

Medical records for 4,319 hospital visits were requested and 3,797 (88%) received. Among children with a diagnosis of prematurity, 25% had received antibiotics. In children 1-5 years of age, diagnoses associated with bacterial infections were more commonly treated with antibiotics (62.4-90.6%) than those associated with viruses (6.3-22.2%). Among pregnant women, 11.1% with vaginal deliveries had been treated with antibiotics and 40.1% of those delivered with Caesarean section.

Conclusions

We have defined the proportion of individual antibiotic treatment for specific inpatient diagnoses. This allows future studies on the association between antibiotics and subsequent disorder, taking separate diagnoses into account.

Key words: antibiotics, epidemiology paediatrics

Key Note:

- Our aim was to assess the proportion of specific inpatient diagnoses treated with antibiotics in pregnant women and children, based on a register-based linkage and nationwide collection of medical records.
- Among children, 25% with prematurity and a larger proportion of diagnoses associated with bacterial infections (62.4-90.6%) than viruses (6.3-22.2%) had received antibiotics
- This information allows future studies on the association between antibiotics and subsequent disorder, taking separate diagnoses into account.

Introduction

The development of antibiotics has enabled treatment of previously life-threatening bacterial infections, and antibiotics are now commonly used to treat children and adults worldwide. Children may be exposed to antibiotics antenatally, during delivery, the neonatal period or first years of life. Since antibiotics given during early life may affect future health in the child (1-4), it is of importance to study how children are exposed both in hospitals and outpatient care. The majority of all antibiotics distributed in Sweden are prescribed in outpatient care, whereas hospitals account for 11% of the total antibiotic use (5). During 2012, 22% of the general population and 27% of children from birth to six-years-of-age received at least one prescription of antibiotics in outpatient care (5), and approximately one of three inpatients receive antibiotics during hospitalisation (6).

Information regarding dispensed antibiotics at an individual level in outpatient care is available through the Swedish Prescribed Drug Register. There is currently no register data covering individual administration of antibiotics to inpatients during hospitalisation and the full individual exposure to antibiotics is therefore unavailable at present. All main and secondary diagnoses during inpatient care are reported to the National Patient Register according to the International Classification of Diseases (ICD) system. Exposure to antibiotics during hospitalisation in relation to infectious diseases and other common inpatient diagnoses can be assessed through medical records.

The aim of this national population-based study was to estimate how diagnoses of infectious diseases and other common diagnoses in the National Patient Register correspond to the use of antibiotics in hospitalised pregnant women and young children.

Material and methods

A cohort of all pregnant women and children from birth to five-years-of-age with a discharge date between 1 July 2005 and 30 November 2011 was identified from the National Patient Register. Start date of pregnancy was estimated from the Medical Birth Register as the date of birth minus gestational age in days. The universal use of the personal identity number enables linkages between the Medical Birth Register, Swedish Prescribed Drug Register and the National Patient Register (7). Linkage between inpatient diagnoses of infectious disease and other common diagnoses in the National Patient Register and dispensed antibiotics (Anatomical Therapeutic Chemical classification system, ATC, J01) in the Swedish Prescribed Drug Register was performed at the National Board of Health and Welfare. To limit the study population to those who had been given antibiotics only in hospitals, all individuals with outpatient dispensed prescription of antibiotics in the Swedish Prescribed Drug Register on the day of discharge or the day after were excluded.

For medical record retrieval, four groups were identified based on children's age at discharge (0-12 months, 1-5 years); prematurity (ICD-codes P072, P073); malformations, factors influencing health status and cerebral palsy (ICD-codes Q, Z and G80); and inpatient diagnoses; as well as a fifth group of pregnant women. Sample size needed for each group and diagnosis was calculated based on clinical assumptions. We aimed at 95% confidence intervals of $\pm 5\%$ from the estimated proportions (percentages) and for the calculations we assumed the proportions in the population were between 10-90%, depending on group and diagnosis. The groups were mutually exclusive. Group 1 comprised children 0-12 months with a diagnosis of prematurity (n=320). Group 2 comprised children 0-12 months without a main or secondary diagnosis of prematurity and without a main diagnosis of ICD-code Q or Z (n=320). Children 1-5 years with inpatient main diagnoses of infectious disease and other common diagnoses specified in Table 1 was defined as Group 3 (n=2,641) and children 1-5

years or without main diagnoses specified in Table 1 was defined as Group 4 (n=320) and finally Group 5 comprised pregnant women with main diagnoses specified in Table 1 (n=718).

Simple random samples (without replacement) of each group 1-5 and diagnosis were drawn by the National Board of Health and Welfare and we were provided with personal identity numbers, date of discharge and name of hospital for the samples to be able to request medical records. The National Board of Health and Welfare also provided the total number of hospital visits for each specified group and diagnosis during the study period (Table S1).

Starting in January 2012, the study participants' medical records, corresponding to the date of discharge from the hospitals for the specific diagnosis of interest, were requested by a letter to the head of the ward where the patient had been treated. Two reminder letters were sent out before the end of data collection in June 2013. Each medical record was manually reviewed and all available information regarding diagnosis and exposure to antibiotics was extracted from text and drug administration records. Antibiotics were further categorised into groups based on ATC-codes when substance name was available.

In total, medical records for 4,319 hospital visits were requested based on a study population of approximately 1.2 million children and pregnant women.

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

Results

We received 3,797 medical records out of the requested 4,319, which correspond to a response rate of 88%. Missing medical records (n=522) belonged to individuals for whom records could not be found at the wards or where the wards did not respond to the request.

Table 1 describes the diagnoses and ICD-10 codes used to identify each group (1-5) and to identify medical records at hospitals in combination with the discharge date. Table 1 also displays the number and proportion of hospital visits with information on treatment with antibiotics (yes, missing). Table S1 displays diagnoses and ICD-10 codes along with descriptive statistics on hospital visits in the total population, requested and received medical records.

In total, 17,750 children between 0 and 12 months had a diagnosis of prematurity. Among the 275 reviewed medical records, 25% had reported treatment of antibiotics, which corresponds to 4,437 children in the total population. Among those with antibiotics recorded, 74.6% also had information on type of antibiotics that could be related to an ATC-code.

In the group of children 1-5 years of age, diagnoses that are commonly associated with bacterial infections were more commonly treated with antibiotics; appendicitis (67.4%), bacterial sepsis (89.6%), meningitis (62.4%), pneumonia (84.9%) and pyelonephritis (90.6%). Diagnoses more often associated with viruses were less often treated with antibiotics; gastroenteritis (8.8%), unspecified viral infections (22.1%), acute bronchitis and upper respiratory tract infections (22.2%) and unspecified abdominal pain (6.3%). The proportion of children treated with antibiotics was not different in the group of children with diagnoses of malformations or cerebral palsy. Among those with antibiotics recorded (n=973), 87.2% also had information on type of antibiotic related to an ATC-code.

Among pregnant women, 334,520 had a vaginal delivery and 11.1% had been treated with

antibiotics according to the 45 reviewed medical records. In the group of women with the most common diagnoses during pregnancy, 16.1% were treated with antibiotics and among those delivered with Caesarean section, 40.1% had been treated with antibiotics. Among those with antibiotics recorded, 83.6% also had information on type of antibiotics.

Discussion

Our results show that a quarter of children below one year of age hospitalised with a diagnosis of prematurity and a high proportion of children with diagnoses of infectious diseases such as bacterial sepsis, pneumonia and pyelonephritis in the National Patient Register are treated with antibiotics in hospital. In children with a diagnosis of virus-associated infections, the proportion treated with antibiotics was lower which reflects treatment guidelines and recommendations (8). We also show that antibiotic treatment is more common in pregnant women delivered with caesarean section than vaginal delivery, and that approximately one sixth of women with the more common diagnoses during pregnancy are treated.

Previous population-based studies have reported point prevalence of antibiotics treatment in inpatient care but not specific to the individual (9,10). In the Swedish Strategic Program against Antimicrobial Resistance (STRAMA) all hospital admissions in selected hospitals were studied for children from birth to 16-years-of-age during two one-week periods and on average 29% of children were exposed to antibiotics (9). Although this is a suitable method on a population level for assessing the risk for antibiotic resistance and the adherence to clinical guidelines, the method is not able to evaluate individual antibiotic exposure for long term follow-up or to study a selected group of patients. There are also ongoing efforts to better understand how to interpret viral findings and to reduce unnecessary use of antibiotics, since infections including acute respiratory illness accounts for a large proportion of all visits to pediatric health facilities (11).

Our study is a population-based study to assess individual antibiotic treatment in hospitals, based on a thorough collection and review of a sample of medical inpatient records from children and pregnant women in national registers with complete coverage. Although there was some missing information on type of antibiotics and exact ATC-codes, we were able to

assess the proportion of antibiotic treatment per diagnosis, which allows future studies on the association between antibiotics and subsequent disorder taking separate diagnoses into account (1-4).

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Table 1. Diagnoses and ICD-10 codes used to define groups 1-5 and descriptive statistics on numbers exposed to antibiotics, along with corresponding numbers with main and secondary diagnoses Q and/or G80 excluded.

Group	Specific diagnosis	ICD 10 codes	Exposed to antibiotics					
			Yes		Missing		Yes*	
			n	%	n	%	n	%
Children 0-12 months								
1	Prematurity	P072, P073	69	25.1	7	2.6	60	24.1
2	Diagnoses other than prematurity	All ICD codes [‡]	49	18.1	11	4.1	46	17.6
Children 1-5 years								
3	Appendicitis	K35	29	67.4	3	7.0	28	66.7
	Chronic tonsillitis	J35	1	3.2	2	6.5	1	3.2
	Gastroenteritis	A08, A09	26	8.8	11	3.7	24	8.4
	Bacterial sepsis	A40, A41	43	89.6	2	4.2	38	88.4
	Meningitis	A87, G00, G02, G03	88	62.4	3	2.1	88	62.4
	Unspecific viral infection	B34	64	22.1	7	2.4	59	21.2
	Pneumonia	J18	242	84.9	5	1.8	222	84.5
	Asthma	J45, J46	6	4.5	4	3.0	6	4.6
	Acute bronchitis and URTI	J20, J21, J06	64	22.2	1	0.4	53	20.0
	Skin infection	L08	57	82.6	-	-	55	83.3
	Seizures	R56	14	6.1	6	2.6	14	6.1
	Unspecific abdominal pain	R10	13	6.3	12	5.8	13	6.4
	Cystitis and pyelonephritis	N30, N10	269	90.6	5	1.7	245	91.1
4	Other main diagnoses than those in group 3		57	21.4	15	5.6	52	21.0
Pregnant women								
5	Maternal diagnoses	O268B, K80, K81, K82, K83, O23, N30, N39, N10, O85	46	16.4	20	7.1	46	16.4
	Vaginal delivery	O80	5	11.1	5	11.1	5	11.1
	Caesarian Section (CS)	O820, O821	71	40.1	14	7.9	70	39.8
	CS (twins) and multiple delivery	O842, O848	55	43.7	9	7.1	55	43.7

[‡] Except P072, P073 as main or secondary diagnoses, and Q or Z as main diagnoses

*Main and secondary diagnosis of malformations and cerebral palsy (ICD-10 Q and G80) excluded.

References

1. Alm B, Erdes L, Mollborg P, Pettersson R, Norvenius SG, et al. (2008) Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics* 121: 697-702.
2. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, et al. (2009) Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 123: 1003-1010.
3. Almqvist C, Wettermark B, Hedlin G, Ye W, Lundholm C (2012) Antibiotics and asthma medication in a large register-based cohort study - confounding, cause and effect. *Clin Exp Allergy* 42: 104-111.
4. Ortqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, et al. (2014) Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ* 349: g6979.
5. Hellman J, Olsson-Liljeqvist B, Bengtsson B, Greko C, editors (2012) SWEDRES-SVARM 2012. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala: Strama.
6. Erntell M, Skoog G (2009) Hur används antibiotika på sjukhus? -PPS 2003, 2004, 2006 och 2008 [Internet]. Strama-Slutenvård.
7. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A (2009) The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 24: 659-667.
8. Craig JC, Williams GJ, Jones M, Codarini M, Macaskill P, et al. (2010) The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. *BMJ* 340: c1594.
9. Erntell M, Skoog G, Cars O, Eriksson M, Skärlund K, et al. (2004) Point prevalence study of antibiotic use in hospitalised pediatric patients in Sweden [Internet]. Strama, SMI.
10. Kimland E, Nydert P, Odling V, Bottiger Y, Lindemalm S (2012) Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. *Acta Paediatr* 101: 772-778.
11. Rhedin S, Lindstrand A, Rotzen-Ostlund M, Tolfvenstam T, Ohrmalm L, et al. (2014) Clinical utility of PCR for common viruses in acute respiratory illness. *Pediatrics* 133: e538-545.